Remarks

The specification is amended to correct U.S. patent application serial and patent numbers.

Claims 1, 3-9, 15-39, 52-54, 77, 85, 88-94, 98 and 107-112 were previously pending in this application.

Claims 3, 4, 6-9, 38, 39, 91, 92 and 94 are now cancelled without prejudice or disclaimer.

Claims 1, 5, 77, 107, 108 and 112 are now amended. Support for the amendment to claim 1 can be found in claims 4, 8 and 9 as originally filed. Claim 5 is amended to depend from a pending claim. Support for the amendment to claims 77, 107 and 112 can be found in each of the claims themselves as previously pending.

New claims 113-120 are now added. Support for new claim 113 can be found in the specification at least in claim 1 as originally filed, and on page 4 lines 15-17, page 11 lines 12-18, page 135 line 32 through to page 136 line 2, and page 133 lines 25-28. Support for claims 114-117 can be found at least in claims 20, 54 and 77 as originally filed, and in the specification at page 67 lines 28-31. Support for new claim 119 can be found at least in claims 1, 4, 8 and 14 as originally filed and in the specification on page 4 lines 15-17. Support for new claim 119 can be found at least in claim 23 as originally filed. Support for new claim 120 can be found at least in claims 1, 4 and 9, and in the specification on page 3 lines 23-26, page 4 lines 15-17, and page 5 lines 7-8.

Claims 1, 5, 15-37, 52-54, 77, 85, 88-90, 93, 98 and 107-120 are pending for examination with claims 1, 113, 118 and 120 being independent claims.

No new matter has been added.

Information Disclosure Statement

The Examiner objects to the form of the citation of an office action from a related application. Applicant respectfully points out that the office action is not a published document and accordingly there is no requirement that it be included in the PTO Form 1449. The Examiner is asked to provide the basis for requiring citation on the PTO Form 1449.

Objection to the Specification

The specification has been objected to for failing to update correctly the recitation of U.S. Patent Applications with U.S. Patents. The specification has been amended to recite that U.S.

Patent Application Serial No. 09/191,170 has now issued as U.S. Patent 6,429,199. The specification has also been amended to correct the U.S. Patent number associated with U.S. Patent Application Serial No. 08/960,774. No new matter has been added.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph

Claims 23 and 24 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 states that the immunostimulatory nucleic acid is "free of unmethylated CpG dinucleotides". The meaning of this phrase is unclear to the Examiner. This phrase intends that the nucleic acid does not contain CpG dinucleotides that are unmethylated. The nucleic acid embraced by this claim however may contain CpG dinucleotides that are methylated.

Claim 24 states that the immunostimulatory nucleic acid is "free of methylated CpG dinucleotides". The meaning of this phrase is unclear to the Examiner. This phrase intends that the nucleic acid does not contain CpG dinucleotides that are methylated. The nucleic acid embraced by this claim however may contain CpG dinucleotides that are unmethylated.

The meaning of these claims is clear and reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

Written Description

Claims 1, 3, 5, 15-39, 52-54, 77, 85, 88-94, 98 and 107-112 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Claim 1 has been amended to recite the limitations from previously pending claims 4, 8 and 9, none of which was rejected for lack of written description.

New claims 113-117 recite that the immunostimulatory nucleic acid is 100% T. The nucleic acids of these claims are structurally defined by sequence, length and backbone composition.

New claims 118 and 119 incorporates limitations from previously pending claims 1, 4 and 8, the latter two of which were not rejected for lack of written description.

New claim 120 incorporates limitations from previously pending claims 1, 4 and 9, the latter two of which were not rejected for lack of written description.

Reconsideration and withdrawal of the rejection is respectfully requested.

Enablement

Claims 1, 3-9, 15-37, 39, 52-54, 77, 85, 88-94, 98 and 107-11

Claims 1, 3-9, 15-37, 39, 52-54, 77, 85, 88-94, 98 and 107-112 are rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably enable the claims.

The Examiner states that the specification is "enabling for a method of stimulating an immune response comprising administering phosphorothioate T-rich immunostimulatory nucleic acid having 100% T nucleotide content that is 8-100 nucleotides in length. Accordingly, new claim 117 is enabled.

Applicant respectfully traverses the rejection of the remaining claims and requests consideration in view of the newly entered amendments. Applicant previously put forth a Wands analysis relating to T-rich immunostimulatory nucleic acids. An updated Wands analysis is provided herewith particularly as it relates to the Examiner's bases for rejection.

Nature of the invention: The invention relates in part to the finding that T-rich nucleic acids can be immunostimulatory. T-rich nucleic acids embrace nucleic acids having greater than 25% T content and/or a poly T motif (i.e., 4 contiguous T nucleotides). Such nucleic acids are immunostimulatory independent of their CpG content. These nucleic acids are capable of activating B cells, NK cells (and thereby enhancing NK-mediated cytotoxicity), NKT cells and monocytes, and inducing release of TNF-α and IL-6.

Breadth of the claims: The claims as amended relate to methods of stimulating immune responses in non-rodent subjects by administering T-rich immunostimulatory nucleic acids comprising particular sequence motifs, length restrictions and optional backbone modifications. Claims 1, 118 and 119 (and claims dependent thereon) recite nucleic acids having a $X_1X_2TTTTX_3X_4$ motif, and optionally being at least 60% thymidine, and claim 113 (and claims dependent thereon) recites nucleic acids that are thymidine homopolymers. Some of the nucleic acids lack an unmethylated CpG motif, commensurate with the finding that T-rich nucleic acids are immunostimulatory even in the absence of unmethylated CpG motifs. The immune

responses may be innate, systemic and/or ADCC-mediated responses. Some claims recite administration of an antigen or an antibody.

The Examiner challenges the breadth of immune response claimed. Such breadth is supported by the application which shows immune indicia that correspond to these varied immune responses, as described herein. The Examiner further challenges the breadth of antigens and antibodies claimed but provides no basis for why such breadth is not enabled. Antigen specific immune responses and ADCC were both known and sufficiently developed at the time of filing. (See for example Weiner reference cited by the Examiner.) The in vitro activities observed for T-rich nucleic acids are involved in adjuvant and ADCC responses in vivo, as discussed herein. (See for example Weiner and Hartmann et al. references cited by the Examiner.)

The Examiner further challenges the breadth of the subject, stating that the claims encompass any subject "including humans for therapy of any pathological disease, including diseases not yet identified". The pending claims relate to stimulation of immune responses and accordingly Applicant does not have a burden of demonstrating therapy of disease.

Level of ordinary skill in the art: The Examiner acknowledges that the level of skill in the art is high. Applicant agrees. Applicant stresses that the level of skill in the art inversely correlates with the amount of guidance and teaching that the Applicant must provide. Accordingly, where the level of skill in the art is high, as in the present technology, the required level of guidance is lowered.

State of the prior art at the time of filing and predictability in the art: The Examiner states that, at the time of filing, immunostimulation by T-rich nucleic acids was a "nascent technology". Applicant agrees as it was the first to document the immunostimulatory capacity of such nucleic acids. With respect to the state and level of predictability in the art of immunostimulatory nucleic acids, Applicant previously directed the Examiner to CpG immunostimulatory oligonucleotides. At the time of filing, the art was aware of CpG motifs that impart immunostimulatory properties to nucleic acids. The ability to make oligonucleotides in general and to use CpG immunostimulatory oligonucleotides in particular was also known at that time, as were in vitro immunostimulation assays (and their relevance to in vivo efficacy). The Examiner however considers this technology to be largely irrelevant to the pending claims. Applicant disagrees. The in vitro immune responses observed with T-rich nucleic acids parallel

those observed with CpG immunostimulatory oligonucleotides (e.g., both nucleic acids stimulate cytokines such as IL-6 and TNF-α and activate NK and B cells, inter alia). Moreover, CpG immunostimulatory oligonucleotides are known to stimulate immune responses in vivo that parallel their in vitro immune response activities. (With reference to CpG oligonucleotides, see, for example, Weiner, cited by the Examiner, page 457: "... it is not surprising that these agents are potent when administered in vivo ..." and "The observed in vivo data fits well with the in vitro data outlined above"; and Hartmann et al. cited by the Examiner, page 1617, Abstract: "... we ... identified in vitro activation of B and NK cells as excellent predictors of in vivo adjuvant activity.") Accordingly, the state of the art at the time of filing was that oligonucleotides that in vitro induce cytokines and activate immune cells (such as those induced and activated by T-rich nucleic acids) are capable of similar activities in vivo.

The Examiner cites a number of references in support of the unpredictability in using T-rich nucleic acids for immunostimulation. For example, the Examiner relies on Agrawal et al. for the teaching that "unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity". Applicant respectfully points out that Agrawal et al. is a reference *directed solely* to CpG nucleic acids, and as such it does not contemplate other classes of immunostimulatory nucleic acids. Thus, taken in the proper context, the teaching of Agrawal more correctly reads " ... the presence of an unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity ..." *of CpG DNA*. Moreover, in citing Agrawal et al., the Examiner has completely disregarded data in the specification showing that non-CpG oligonucleotides are immunostimulatory. (See for example FIG. 4 which shows that non-CpG ODN 5126, 2137 and 2117 are immunostimulatory.) These data evidence that T-rich nucleic acids can be immunostimulatory independent of their CpG content.

The Examiner cites Hartmann et al. for the teaching that "To have clinical utility, ODN must be administered in a form that protects them against nuclease degradation." The teaching of Hartmann et al. refers to increasing the half-life of ODN in humans, presumably to reduce the amount of ODN administered. ODN with shorter half-lifes however can be administered at higher doses in order to observe in vivo effects. Alternatively, ODN can be formulated to reduce nuclease degradation. It is therefore possible to stimulate immune responses in vivo using T-rich nucleic acid even in the absence of a backbone modification such as a phosphorothioate modification.

The Examiner cites Vollmer et al. for the teaching that polythymidine ODN must be at least 21 nucleotides to be immunostimulatory, that "non-CpG T-rich ODNs are always less efficient and potent than CpG ODNs", and that the mechanism of action by non-CpG "remains to be elucidated". Applicant traverses each point. First, the Examiner has disregarded the data in the specification that shows that a thymidine homopolymer that is 18 nucleotides in length activates B cells in vitro. (See FIG. 5., ODN 2196.) Second, Applicant maintains that the results of Vollmer et al. are dosage specific and that for every T-rich nucleic acid there is an optimal dose which may not be reflected in the data of Vollmer et al. In support thereof, the Examiner is directed to FIG. 1 of Vollmer et al. which shows immunostimulation by a T-rich nucleic acid that is 17 nucleotides in length (ODN 5192). The dose-response data for this nucleic acid demonstrate that its stimulatory capacity increases substantially with increasing dose. Similarly, FIG. 5 of the instant specification shows that at doses higher than those tested in Vollmer et al. the activity of a thymidine homopolymer 18 nucleotides in length approaches that of longer thymidine homopolymers. Thus, the data highlighted by the Examiner in FIG. 2 of Vollmer et al. corresponds to a *single dose* and there is no indication that it is necessarily the optimal dose for the nucleic acids tested. Third, the fact that non-CpG T-rich ODNs may be less immunostimulatory than CpG ODNs under some conditions is not relevant to patentability. Applicant need only show that the claimed method achieves its intended result, not that it achieves a better result than prior art methods. Applicant has met this burden by demonstrating that non-CpG T-rich ODN are immunostimulatory. Finally, understanding mechanism is not a prerequisite to patentability.

The Examiner cites McCluskie et al. for the teaching that "a polythymidine nucleic acid twenty nucleotides in length ... did not have an immunostimulatory effect in immunized mice." As previously stated, the data of McCluskie et al. correspond to a single dose of a T-rich nucleic acid. Presumably, it is a dose at which the tested CpG nucleic acids were active. However, as argued herein, that dose may not be optimal for a non-CpG nucleic acid such as a non-CpG T-rich nucleic acid. The instant specification teaches that the optimal immunostimulatory doses for non-CpG T-rich nucleic acids can result in decreased activity for CpG nucleic acids. This observation supports the idea that the McCluskie et al. data correspond to optimal CpG nucleic acid doses that are not necessarily optimal non-CpG T-rich nucleic acid doses. Similarly the teaching of Jones et al. can be qualified since only a single dose of nucleic acid was used and that

dose was optimized for CpG nucleic acid effect. Vollmer et al., McCluskie et al. and Jones et al. therefore stand for the proposition that higher doses of non-CpG T-rich nucleic acids may be necessary for immune stimulation (as compared to CpG nucleic acids). They do not stand for the proposition that short non-CpG T-rich nucleic acids are not immunostimulatory, as asserted by the Examiner.

Vollmer et al. is further cited for a teaching regarding routes of administration. However, this passage actually cites McCluskie et al. (discussed herein) and another CpG-oriented reference. Respectfully, both references provide results optimized for CpG immunostimulation and thus do not reflect optimized assays for T-rich nucleic acids.

The Examiner cites Weiner as evidence of unpredictability of CpG nucleic acid immunostimulation and then questions the extrapolation of CpG art to T-rich nucleic acids. The Examiner has taken the teachings of Weiner out of context; when taken in its entirety, Weiner summarizes the in vitro and in vivo immunostimulatory effects of CpG ODN. For example, Weiner states that "it is now clear that ... CpG ODN are potent immunostimulatory agents ..." and "it is clear that CpG ODN act rapidly on a variety of cell types (including) activation of B cells, natural killer cells, and antigen-presenting cells ..." Weiner further states that "preliminary results from clinical trials using CpG ODN as an immune adjuvant are promising. Preclinical studies suggest CpG ODN can also enhance innate immunity against a variety of infections, synergize with monoclonal antibodies to enhance antibody-dependent cellular cytotoxicity ..." With respect to the heterogeneity of sequences and cell types activated, Weiner teaches that CpG ODN can be classified according to their immune stimulation profile. It does not teach that CpG ODN are not immunostimulatory. As stated above, the immune stimulatory profiles of CpG ODN and T-rich nucleic acids are similar in terms of immune cells activated and cytokines induced. The fact that T-rich nucleic acids may be less immunostimulatory than CpG ODN under some conditions should not prevent extrapolation from CpG to T-rich nucleic acid immunostimulation.

Working examples and guidance in the specification: Applicant directs the Examiner to Table G and FIGs. 4-12 which document the activity of ODNs 2117, 2137, 2130, 5126, 3041, 2183, 2194, 2196 and 5162 in NK cell activation and killing, B cell activation, NKT cell activation, monocyte activation, and TNF-α and IL-6 induction.

The ability to stimulate B cells and NKT cells correlates at least with a role in adaptive (or antigen-specific) immunity in vivo. (See Hartmann et al., abstract, which states that B and NK activation in vitro is predictive of adjuvant activity in vivo.) The ability to stimulate NK cells correlates at least with a role in adaptive immunity and more particularly a role in ADCC in vivo. (See Weiner, page 460 right column, which states that ADCC is mediated by NK cells and monocytes/macrophages.) The ability to induce TNF-α and IL-6 correlates at least with a role in innate immunity in vivo. The ability to stimulate monocytes correlates with a role in both adaptive and innate immunity.

The in vitro activities of T-rich nucleic acids parallel those of CpG ODN. Weiner teaches that the in vitro activities observed for CpG fit well with their observed in vivo activities. It follows then that a reasonable correlation exists between the demonstrated in vitro activities of T-rich nucleic acids and the claimed in vivo methods.

Quantity of experimentation: The quantity of experimentation needed to make and use the invention, in view of the disclosure and the state of the art at the time of filing, is not beyond the level of experimentation routinely practiced by persons of ordinary skill in the art, particularly where the level of skill is high. The specification provides the parameters that define a T-rich immunostimulatory nucleic acid both structurally and functionally, as well as species thereof. It further teaches how to formulate and administer the nucleic acids for immune stimulatory purposes. To the extent that parameters must be optimized, particularly in a clinical setting, such optimization is routine in the medical arts.

The Examiner uses Genentech, Calgene and National Recovery Technologies to support his position that undue experimentation is required to practice the claimed invention. Genentech 108 F.3d at 1366; Calgene 188 F.3d at 1374; National Recovery Technologies 166 F.3d at 1198. These cases are factually distinct from the instant application. For example, in Genentech, the Court found that the specification at issue "does not describe *in any detail whatsoever* how to make hGH using cleavable fusion" and "does not describe a *specific material* to be cleaved or any reaction conditions under which cleavable fusion expression would work" (emphasis added). The instant specification can be distinguished from the specification in Genentech at least based on the level of detail and particularity provided therein. The claimed invention relates to specific immunostimulatory nucleic acids comprising defined nucleotide sequences and their use in immune response induction. The claims recite the minimal nucleotide

sequence. Methods of making nucleic acids of defined sequence were known in the art at the time of filing. The specification teaches how to formulate, administer and dose the nucleic acids of the claims.

In National Recovery Technologies, the Court concluded that the patent at issue "recognizes a specific need ... and suggests a *theoretical* answer to that need" (emphasis added). This is the not case in the instant application. As outlined above, the instant application recognizes a specific need but it also provides an *actual* answer to that need via the detailed disclosure of immunostimulatory nucleic acids and methods of use (and data in support thereof).

In Calgene, the claims at issue related to *any* cell containing *any* antisense molecule, and methods of regulating gene expression in *any* cell using *any* antisense molecule while the specification demonstrated effect in only one cell type. The Calgene Court considered antisense technology to be "highly unpredictable". The instance case differs. First, the instant claims recited nucleic acids comprising a defined sequence. Second, Applicant has demonstrated effects of the claimed nucleic acids on a number of immune cells. Third, immunostimulation by nucleic acids was known and thus was not a highly unpredictable art at the time of filing.

Accordingly, in view of the foregoing, the specification together with the state and knowledge in the art at the time of filing enables the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 38

Claim 38 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

Without conceding to the Examiner's position, but rather for the sake of expediting prosecution, Applicant cancels claim 38 and dependent claim 39.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102(b)

Claims 1, 3-7, 15-16, 18-19, 21-25, 77, 85, 88-92, 94 and 112 are rejected under 35 U.S.C. §102(b) as anticipated by Liang et al. (J. of Clinical Investigation, 98(5):1119-1129, 1996).

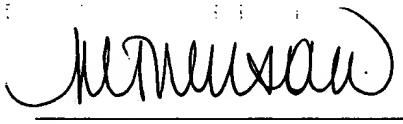
Applicant respectfully traverses. Liang et al. report the effects of a fully phosphorothioated thymidine homopolymer 20 nucleotides in length on immune cells in vitro. Liang et al. does not administer the oligonucleotide to a subject. Accordingly, Liang et al. does not anticipate the pending claims, all of which relate to immune stimulation in vivo following administration of a T-rich oligonucleotide.

Reconsideration and withdrawal of the rejection are respectfully requested.

Summary

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance or has any questions or comments, he is requested to call the Applicant's representative at the telephone number listed below.

Respectfully submitted,



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